Interleukin 12 (IL-12) (MEDI1191)

Last program update: May 6, 2021

Phase 1 study of MEDI1191 ongoing; study run by AstraZeneca
Preliminary data from Phase 1 presented at the ESMO Targeted Anticancer Therapies Virtual Congress in March 2021
mRNA-encoding IL-12 (MEDI1191)
mRNA-encoded cytokine to activate tumor microenvironment
IL-12 (MEDI1191) overview

Powerful immunomodulatory cytokine well-suited for local delivery

Species: Mouse

- IL-12: potent immune modulator typically associated with a type 1 immune response and production of interferon-gamma

- Clinical development of systemically administered recombinant IL-12 has been hampered by systemic toxicity

- We have demonstrated well-tolerated intratumoral doses of IL-12 mRNA induce complete responses in multiple mouse models of cancer, exert abscopal effects on distal tumors, and yield protective immunity

- Clear rationale for the combination of IL-12 and PD-1/PD-L1 blockade

Modernat concept: Intratumorally-administered mRNA encoding IL-12 to activate tumor microenvironment
Preliminary safety, antitumour activity and pharmacodynamic results of the Human Intratumoral Immunotherapy (HIT-IT) trial of MEDI1191 (mRNA IL-12) in patients with advanced solid tumours and superficial lesions

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Declaration of interests

Omid Hamid, MD

Consulting/Advisory Boards
Aduro, Akeso, Amgen, BeiGene, BioAtla, Bristol Myers Squibb, Roche Genentech, GlaxoSmithKline, Immunocore, Idera, Incyte, Janssen, Merck, NextCure, Novartis, Pfizer, Sanofi/Regeneron, Seattle Genetics, Tempus, Zelluna

Speakers’ Bureaus
Bristol Myers Squibb, Novartis, Pfizer, Sanofi/Regeneron

Contracted Research (For Institution)
Arcus, Aduro, Akeso, Amgen, BioAtla, Bristol Myers Squibb, CytomX, Exelixis, Roche Genentech, GlaxoSmithKline, Immunocore, Idera, Incyte, Iovance, Merck, Moderna, Merck-Serono, NextCure, Novartis, Pfizer, Sanofi/Regeneron, Seattle Genetics, Torque, Zelluna
MEDI1191 (IL-12 mRNA) promotes antitumour immunity via multiple mechanisms

- IL-12 mRNA uptake, translation & IL-12 release
- Tumour Cell Killing
- Tumour Cell
- IL-12
- IL-12 receptor
- NK cell
- ACTIVATION
- PD-L1 (tumor / leukocytes)
- (CXCL10) T-Cell Recruitment
- Lipid nanoparticle containing IL-12 mRNA
- Tumour macrophages/dendritic cells
- IFN-γ
- IFN-γ receptor
- Antigen Presentation
- CD4+/CD8+ T cell
- Antigen-presenting cell


CD, cluster of differentiation; IFNγ, interferon gamma; IL-12, interleukin-12; mRNA, messenger ribonucleic acid; NK, natural killer.
Dosing scheme

**Part 1A** Sequential
MEDI1191 + durvalumab

- **Screening**
- MEDI1191 IT dosing
- MEDI1191 IT dosing
- Durvalumab IV infusion
- Durvalumab IV infusion
- Durvalumab IV infusion

Biopsy

Day -28
Day 1
Day 22
Day 43
Day 71
Day 99

DLT assessment
Disease assessment and biopsy

**Part 1B and 1D** Concurrent
MEDI1191 + durvalumab

- **Screening**
- MEDI1191 + durvalumab
- MEDI1191 + durvalumab
- MEDI1191 + durvalumab
- Durvalumab
- MEDI1191 + durvalumab

Biopsy

Day -28
Day 1
Day 29
Day 57
Day 85
Day 113

DLT assessment
Disease assessment and biopsy

**D Q4W**

**MEDI1191 Q8W**
Study design

Part 1 (Escalation)

Part 1A
- Sequential M+D dose level 1 C/SC lesions
- Sequential M+D dose level 2 C/SC lesions
- Sequential M+D dose level 3 C/SC lesions
- Sequential M+D dose level 4 C/SC lesions
- Sequential M+D dose level 5 C/SC lesions
- Sequential M+D dose level 6 C/SC lesions

Part 1B
- Concurrent M+D C/SC lesions
- Concurrent M+D C/SC lesions
- Concurrent M+D C/SC lesions
- Concurrent M+D Deep-seated lesions

Part 1D
- Concurrent M+D Deep-seated lesions
- Concurrent M+D Deep-seated lesions
- Concurrent M+D Deep-seated lesions
- Concurrent M+D Deep-seated lesions

Part 2 (Expansion)

Other expansion cohorts will be based on efficacy

- Concurrent MEDI1191 + durvalumab in NSCLC (C/SC/supraclavicular) n=10
- Concurrent MEDI1191 + durvalumab in NSCLC (deep-seated) n=30

Key eligibility criteria

- ≥1 C/SC lesion or ≥2 deep-seated lesions suitable for IT injection, and ≥1 noninjected lesion measurable by RECIST v1.1
- Part 1: histologically or cytologically confirmed advanced solid tumours that have progressed on or are refractory to ≥1 line of standard systemic therapy for recurrent/metastatic disease*
- Part 2: histologically or cytologically confirmed locally advanced or metastatic NSCLC that has progressed on or is refractory to ≤2 lines of standard of care therapy for recurrent/metastatic disease, including anti-PD-1/PD-L1 and anti-CTLA-4 immunotherapy*

C, cutaneous; IT, intratumoural; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; RECIST, Response Evaluation Criteria in Solid Tumors; SC, subcutaneous
* A line of therapy is defined as systemic therapy given in the recurrent/metastatic setting with palliative intent.
### Patient characteristics and treatment exposure

<table>
<thead>
<tr>
<th></th>
<th>As Treated Population (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td>Male / Female</td>
</tr>
<tr>
<td><strong>Mean age (range), years</strong></td>
<td>51.7 (18–68)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>7 (70.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Multiple/other</td>
<td>2 (20.0)</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td>5 (50) / 5 (50)</td>
</tr>
<tr>
<td><strong>Previous immunotherapy, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>6 (60.0)</td>
</tr>
<tr>
<td>Previous PD-1 inhibitor therapy</td>
<td>5 (50.0)</td>
</tr>
<tr>
<td>Previous PD-1 + CTLA-4 inhibitor combination therapy</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td><strong>Tumor type, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Head and neck squamous cell carcinoma</td>
<td>2 (20.0)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2 (20.0)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Non-small-cell lung cancer</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Gastric</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (30.0)</td>
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<tr>
<td><strong>Median number of doses of MEDI1191 (range)</strong></td>
<td>2.0 (1.0, 2.0)</td>
</tr>
<tr>
<td><strong>Median number of doses of durvalumab (range)</strong></td>
<td>8.0 (4.0, 21.3)</td>
</tr>
</tbody>
</table>

Data cutoff: 28 Jan 2021

ECOG PS, Eastern Cooperative Oncology Group performance status; HNSCC, head and neck squamous cell carcinoma; SD, standard deviation; WHO, World Health Organization

*A line of therapy is defined as systemic therapy given in the recurrent/metastatic setting with palliative intent*
# Safety Summary: Part 1A MEDI1191 + durvalumab

- No DLTs
- No Grade ≥3 TRAEs or TR SAEs
- NR TESAEs: worsening constipation, oesophagitis, ascites (2x), gastric stenosis, sepsis

<table>
<thead>
<tr>
<th>Treatment-emergent grade 3/4 AEs (none treatment-related)</th>
<th>Dose level 1 n=4</th>
<th>Dose level 2 n=3</th>
<th>Dose level 3 n=3</th>
<th>Total N=10</th>
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<tbody>
<tr>
<td>Patients with ≥1 event, n (%)</td>
<td>2 (50)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
<td>4 (40)</td>
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<tr>
<td>Abdominal pain</td>
<td>1 (25)</td>
<td>0</td>
<td>0</td>
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<td>Ascites</td>
<td>1 (25)</td>
<td>0</td>
<td>1 (33)</td>
<td>2 (20)</td>
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<td>Gastric stenosis</td>
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<td>0</td>
<td>1 (33)</td>
<td>1 (10)</td>
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<td>Oesophagitis</td>
<td>0</td>
<td>0</td>
<td>1 (33)</td>
<td>1 (10)</td>
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<tr>
<td>Fatigue</td>
<td>1 (25)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Hyponatraemia</td>
<td>1 (25)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Dyspnoea</td>
<td>1 (2.5)</td>
<td>0</td>
<td>0</td>
<td>1 (10)</td>
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<tr>
<td>Sepsis</td>
<td>0</td>
<td>1 (33)</td>
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<td>1 (10)</td>
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Part 1A Cohort 2: MEDI1191 induces pharmacodynamic changes in periphery and tumour consistent with proposed mechanism of action

**Peripheral blood**

<table>
<thead>
<tr>
<th>IL-12 (pg/mL)</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
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<tbody>
<tr>
<td>D1 predose</td>
<td>8</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>D2</td>
<td>16</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>D3</td>
<td>16</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>D4</td>
<td>16</td>
<td>16</td>
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<tr>
<td>D5</td>
<td>16</td>
<td>16</td>
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**IFNγ (fold change)**

<table>
<thead>
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<th>IFNγ (fold change)</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
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<tr>
<td>D1 predose</td>
<td>0.5</td>
<td>0.25</td>
<td>0.125</td>
</tr>
<tr>
<td>D2</td>
<td>16</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>D3</td>
<td>16</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>D4</td>
<td>16</td>
<td>16</td>
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<tr>
<td>D5</td>
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**Tumour**

**Transcriptomics**

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<th>SCR D15</th>
<th>D15 D15</th>
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<td>Angiogenesis</td>
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<td>Tregs, T, IO, T3</td>
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<td>CTLA4</td>
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<td>Nkx2, T</td>
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<td>C2274</td>
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<tr>
<td>Nkcells.Danaher.IO_T2</td>
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<td>Th2</td>
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<td>IL12A</td>
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<td>IL12RB1</td>
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<td>CD4</td>
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<td>T, cell exhaustion, Med, IO, T4</td>
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<td>PDDC1</td>
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<td>CD8Tcells.Danaher.IO, T3</td>
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<td>Exhausted</td>
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<tr>
<td>IFNγ</td>
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<tr>
<td>CD8</td>
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Red box = PR in melanoma pt; Data cutoff: 28 Jan 2021
ECOG PD, day; IFNγ, interferon gamma; IL-12, interleukin-12; SCR, screening
Partial response #1: Case summary

- 55-year-old male; ECOG PS 1
- Stage IVa HNSCC; PD-L1 negative
- Low tumour mutation burden (<20 muts/Mb) by ctDNA
- 4 prior regimens including nivolumab
- Part 1A Cohort 1: 1 cycle of MEDI1191 and 5 cycles of durvalumab on study
- Injected lesion: right cervical lymph node (20 Sept, 2019)
- ~58.7% change in size of target (noninjected) lesions along with shrinkage of injected (nontarget) lesions after 1 cycle of MEDI1191 and 4 cycles of durvalumab

HRAS and PIK3CA driver mutations not detected at the last time point

ctDNA, circulating tumour DNA; HNSCC, head and neck squamous cell carcinoma; muts/Mb, mutations/megabase
Partial response #2: Case summary

- 63-year-old male; ECOG PS 0
- Stage IV anal melanoma; PD-L1 negative
- Low tumour mutation burden (<20 muts/Mb) by ctDNA
- 3 prior regimens including nivolumab + ipilimumab and pembrolizumab monotherapy
- Part 1A Cohort 2: 2 cycles of MEDI1191 and 6 cycles of durvalumab on study
- Injected lesion: Left buttock SC nodule (20 July and 12 Aug, 2020)

- 61.2% change in size of noninjected (target lesions) along with shrinkage of nontarget (injected) lesions after 2 cycles of MEDI1191 and before first durvalumab dose
Conclusions

- Ten patients with advanced solid tumors and superficial lesions have been enrolled.
- No dose-limiting toxicities; No ≥ grade 3 TRAEs.
- Two PRs have been observed [HNSCC and melanoma].
- Both responders were previously PD-1 +/- CTLA4-treated.
- Response in injected, local, and distant non-injected lesions.
- Melanoma PR seen early with MEDI1191 alone.
- Melanoma PR in correlative studies showed increase in IFN gamma, IL-12, and inflammatory transcriptome.
- Study ongoing, with the combination treatment to be tested in concurrent combination and in deep-seated lesions.
Acknowledgements

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